## REMARKS

In non-final Office Action mailed April 11, 2001, the Examiner entered applicants' amendment filed January 17, 2001 and acknowledged the applicants' provisional election with traverse of Group I. The Examiner made final the requirement for restriction and withdrew Claims 10-25 from further consideration as being drawn to a non-elected invention. Claims 1-9 and 26-29 remain under consideration.

A petition to correct inventorship in the application is being submitted under separate cover. The petition reflects a determination that an additional inventor is appropriately named in view of subject matter newly claimed in the applicants' prior response.

The Examiner rejected Claims 1, 3, 4, 5, 6, 8, 9, and 26 for obviousness-type double patenting over Claims 1-3 and 6 of US Patent No. 5,780,236. The Examiner rejected the claims under 35 U.S.C. §112, first paragraph for alleged overbreadth. Claims 1, 3-6, 8, 9, and 26 are rejected under 35 U.S.C. §102(a) as being allegedly anticipated by Bilger et al. Claim 2 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Bilger et al. in combination with Rinchik et al. (1990). Claim 27 is rejected under §103(a) as allegedly obvious over Bilger et al. in combination with Dietrich et al.

For the reasons noted below, the applicants traverse the rejections and respectfully request reconsideration of the merits of this patent application.

A petition for one month extension of time accompanies this response so the response will be deemed to have been timely filed. Should any additional extension of time be due in this or any subsequent response, please consider this to be a request for the appropriate extension of time and a request to charge the required fee to Deposit Account No. 17-0055. No other fee is believed due. However, should any other fee be due in this or any subsequent response, please charge the fee to the same deposit account.

Each issue raised by the Examiner is considered separately below.

Requirement for Restriction

In the response filed January 17, 2001, the applicants provisionally elected Group I with traverse. The Examiner was not persuaded by the applicants' traversal and made final the requirement for restriction. The applicants respectfully request reconsideration of the refusal to join Groups I and II. If the Examiner were to consider and search Claim 10 (Group II), the Examiner will necessarily search for art relating specifically to the breeding methods of the outcrossing, backcrossing, and verifying steps of that claim. All of the elements of those three steps are recited in Claim 1 and its dependents (Group I). The fact that Claim 1 recites certain limitations, namely the gender of the founder and inbred strain animals and the congenic nature of the dominant allele, does not put those three claim elements outside the scope of those related elements recited in Claim 10. There is no prohibition against

examining related claims in the same application even when the patentability analysis could lead to different results in different claim sets. On the other hand, to separate Group II from Group I imposes a substantial burden upon the applicants who must pay additional filing fees, prosecution costs, issue fees, and maintenance fees. For these reasons, the Examiner is respectfully asked to again reconsider including Group II in further prosecution of the provisionally elected Group I.

Double Patenting

Claims 1, 3, 4, 5, 6, 8, 9, and 26 are rejected for obviousness-type double patenting over Claims 1-3 and 6 of US Patent No. 5,780,236, the parent of this CIP patent application. The Examiner asserts that the patented steps and the outcrossing, backcrossing, and verifying steps of the claimed invention are the same. The applicants respectfully traverse the Examiner's assertion. The steps in the claims are not the same. Specifically, in the patented method, a first cross is performed and the progeny of that cross are examined for the appearance of an outlying phenotype. Then, a founder mouse whose progeny have an outlying phenotype are crossed to a wild-type (e.g., unmutagenized) mouse of the founder strain. The salient distinction between the patented method and pending claim 1 is the number of mouse generations required to detect the outlying phenotype. In the former, two generations are employed: first, mutagenized males are bred to normal (unmutagenized) females to produce a holding generation (G1); second G1 animals are outcrossed to an index strain to produce mice for screning. In the pending claims, mutagenized males are bred directly to the index strain to produce mice for screening. To preserve new mutations of interest, gametes from candidate carriers are preserved. Moreover, the animals that result from the two methods are genetically different.

This substantial difference in method design yields the substantial advances described in the applicants' arguments filed April 11, 2000. It is not accurate to say, as the Examiner has said, that the steps "are the same," nor has the Examiner argued why the pending claims are either encompassed by the patented method or made obvious by the patented method.

Reconsideration is respectfully requested.

Rejections Under §112, first paragraph

The Examiner rejected Claims 1-9 and 26-29 for alleged overbreadth and lack of enablement. The Examiner takes issue with the asserted scope of the claims as encompassing "any and all non-human animals and any and all genetic loci." Putting aside for the moment the asserted overbreadth, applicants point out that Claims 26-29 refer specifically to a particular index allele at a particular genetic locus in a single inbred mouse strain. These claims were submitted in response to a request from the Examiner for narrow claims that

could be readily examined. At the very least, it is believed that these claims should not be subject to the rejection under §112, first paragraph. Indeed, the Examiner acknowledges in making the rejection that the specification is "enabling for a mouse and a murine genetic locus," namely that recited in Claims 26-29.

Looking beyond the embodiments of Claims 26-29, the applicants also point out that the claims do not extend to any and all non-human animals, but only to those for which there exist inbred strains. By their very nature, inbred strains are homozygous at all loci and the genetic behavior of those strains is predictable. So by the very terms of the claims, one cannot merely procure any non-human animal for use in the method, but must choose the starting materials from a well defined class of animals, the genetic nature of which is important to the skilled artisan. Likewise, the index allele cannot be at any and all genetic loci, but rather only an allele at a locus known to confer an index phenotype when carrying a congenic dominant allele. The skilled artisan can readily choose a dominant allele at such a locus for use in the method, although it is the subsequent practice of the invention that yields, by phenotypic analysis, a modifier of that dominant allele.

In maintaining the rejection, the Examiner asserts that the specification does not provide sufficient guidance as to what effect the mutagen would have on the genotype and phenotype of any and all non-human animals or whether the mutation would be preserved through the enabled breeding regimen of the claimed invention such that the method for identifying a segregating mutation would be enabled. The claims require the founder inbred strain to carry random point mutations, without regard to the method by which those mutations are introduced. One can readily depend upon the ability of the skilled artisan to introduce random point mutations into the genome of all inbred animals suitable for use in the method. The ability to introduce mutations into the genome of inbred animals is part and parcel of the work done by the skilled artisan in this field. The effect of a mutagen on a genotype is something that must be addressed in every breeding trial and, by its very nature, it is impossible to predict every such effect. Nonetheless, the science of genetics has forged ahead and the applicants here should not be held to any higher standard than that to which the skilled artisan is held. More to the point, the power and desirability of the claimed method arises largely from the inability to know in advance the effect of a mutagen or point mutation on the phenotype conferred by the index allele. It is by harnessing that power in the method that the user can identify subtle changes in that phenotype and proceed from those phenotypic observations to isolate a modifier of the index phenotype.

The Examiner also questions whether the specification provides sufficient guidance as to whether the mutation would be preserved through the breeding regimen. This too can be raised as an issue in any breeding protocol and does not require particular comment when applied to the claimed method. Certainly it is generally the case that a mutation fixed in the

genome is transmitted according to the rules of Mendelian genetics and should be maintained simply by practicing the breeding and selection methods described by the applicants. Surely all breeding methods are subject, at some level, to reversion and hypermutation, but these are the norms of practice in the field and not aspects or shortcomings of the claimed invention.

While it is not unreasonable to desire duplication of the method by the applicants in a second species, the Examiner will surely appreciate the very practical limitations imposed upon a laboratory engaged in efforts to practice and improve the claimed methods in a single species. Even so, however, the applicants have here countered the Examiner's overly broad and general suggestions that experimentation undue for one skilled in the art is required to transfer the claimed technology to other inbred animals. However the Examiner has not considered the claims from the perspective of a skilled artisan. For that reason, reconsideration of the rejections under §112, first paragraph is respectfully requested.

Rejections Under §102

Claims 1, 3-6, 8, 9, and 26 are rejected under §102(a) as being anticipated by Bilger et al. In short, the applicants traverse the rejection based upon Bilger both because the animals crossed by Bilger do not meet the limitations of independent Claim 1 and because the differences in those mice that result in products of the method that are substantially different from those produced in the claimed method. With regard to the Examiner's comment that "there is no recitation of crossing B6-*Min* mice either to mutagenized animals or to isogenic animals containing only random point mutations," applicants clarify that the cross in Bilger is a cross between an index inbred strain and a different inbred strain. In contrast, the claims recite crossing an index inbred strain to an animal that carries random point mutations relative to a wildtype animal of the founder inbred strain. A suitable animal can be a mutagenized inbred animal or an isogenic animal containing random point mutations. Both possibilities are embraced within Claim 1; the latter possibility is specified in Claim 8. Bilger et al. describe crosses between inbred strains that reveal the presence of polymorphic modifiers (not single point mutation modifiers) of an index phenotype (Min). The cross involving the BTBR strain in Bilger et al. demonstrated that BTBR carries a sensitive allele at such a locus, Mom1. Mom1 is complex, unlike potential point mutagen-induced modifiers identified in the methods of this invention which result from single base pair changes. Claims 6, 8, 9 and 26 warrant further mention. Claim 6 further recites that both the index inbred strain and the founder inbred strain share an isogenic genetic background. This is certainly not the case between B6 mice (or B6-*Min* which carries a dominant index allele) and BTBR mice. The substantial genetic differences in the genetic stock of these two different inbred strains represented a significant shortcoming in the prior art that can be avoided using the claimed methods.

Claim 8 recites producing the founder inbred mouse strain carrying random point mutations by treating a wildtype inbred mouse with a mutagenic agent to induce point mutations. Claim 9 specifies a particular mutagenic agent. As was noted above in connection with Claim 1, this step is absent from Bilger et al. In Bilger, the index strain containing the dominant allele was crossed to wildtype BTBR mice. Those mice were not treated with a mutagenic agent to induce point mutations.

Claim 26 is a particular embodiment of Claim 6 where both inbred strains share an isogenic background. In Claim 26, that background is the B6 (more formally referred to as C57BL/6) background. In Claim 26, a female B6 mouse congenic for the *Min* allele at the Apc locus is crossed to a male B6 mouse carrying random point mutations. Since Bilger et al. describe a cross between B6-*Min* mice and wildtype inbred BTBR mice, it is not apparent to the undersigned how this claim could possibly be anticipated by Bilger et al., since the crossed germplasms is not the same. For all these reasons, reconsideration of the rejections under §102(a) is respectfully requested.

Rejections Under §103

Claim 2 is rejected under §103(a) as being unpatentable over Bilger et al. taken with Rinchik et al. For the reasons noted above, the basis for the rejection over Bilger is flawed. Moreover, the Examiner has not argued that any disclosure in Bilger beyond that cited under 102(a) would disclose, teach, or suggest the changes in breeding strategies disclosed by the applicants. For this reason, the rejection of Claim 2 cannot stand, whether or not it is combined with Rinchik et al. Hence, whether or not the prior art suggests using stored gametes, the cited art taken as a whole does not disclose, teach, or suggest the claimed breeding method.

Claim 27 is also rejected under §103(a) as being unpatentable over Bilger et al. with Dietrich et al. As in the rejection under §102(a) and in the prior rejection under §103(a), the rejection based upon Bilger is flawed and cannot support a rejection of Claim 27 even when applied in combination with Dietrich. Claim 27 incorporates the limitations of Claims 26, 6 and 1. The distinctions of those claims from Bilger et al. is also discussed in connection with the §102 rejection.

For all of these reasons, reconsideration of the rejections under §103 is respectfully requested.

In view of the preceding argument, reconsideration of the merits of the patent application is respectfully requested. Should any issues remain outstanding, the Examiner is

invited to contact the undersigned directly to schedule a person or telephonic interview.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

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Title: METHOD FOR IDENTIFYING MUTANTS AND MOLECULES

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1. (Twice Amended) A method for identifying a segregating single point mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing at least one male animal of a non-human founder inbred strain to at least one female animal of a non-human index inbred strain to obtain F1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, wherein at least one of the F1 progeny that carry the dominant allele also carry at least one random mutation;

backcrossing gametes from male F1 progeny to at least one female of the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype; and

verifying that the outlying phenotype is caused by a segregating single point mutation.

2. A method as claimed in Claim 1 wherein any of the crosses employ preserved gametes.

3. A method as claimed in Claim 1 wherein the $F_1$ progeny and some of the N2 progeny exhibit an extreme outlying phenotype.

4. A method as claimed in Claim 3 wherein the segregating mutation is a heterozygous modifier of the index phenotype selected from a group consisting of an enhancing modifier and a suppressing modifier.

5. A method as claimed in Claim 1 wherein the dominant allele is a *Min* allele at an *Apc* locus in a mouse.

6. A method as claimed in Claim 1 wherein the index inbred strain and the founder inbred strain share an isogenic genetic background.

7. A method as claimed in Claim 6 further comprising the step of mapping the segregating mutation using a mapping partner strain produced by the steps of:

treating an animal of an index strain with a mutagenic agent to induce point mutations in the treated animal;

crossing the treated animal to an animal of the index strain to produce F1 progeny; and

sib-mating F1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.

8. A method as claimed in Claim 1 wherein the founder inbred mouse strain is produced by a method comprising the step of treating a wild-type inbred mouse with a mutagenic agent to induce point mutations.

9. A method as claimed in Claim 8 wherein the mutagenic agent is ethylnitrosourea.

26. A method as claimed in Claim 6 wherein the method identifies a segregating mutation at a genetic locus that modifies tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the method comprising the steps of:

outcrossing at least one male C57BL/6 mouse carrying random point mutations to a female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain F1 progeny, wherein at least one of the F1 progeny carries both the *Min* allele and a random point mutation; and

backcrossing gametes from male F1 progeny to at least one female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny carries the *Min* allele and has a tumor multiplicity that is modified relative to tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the modified tumor multiplicity being characteristic of the segregating mutation.

27. A method as claimed in Claim 26 wherein the modified tumor multiplicity is evaluated according to a method comprising the steps of:

repeatedly applying for random permutations of mice among N2 backcross subkindreds a likelihood ratio test of the null hypothesis that no multiplicity modifier is

segregating to obtain a p-value, wherein a p-value of less than 0.05 indicates a potential carrier of the segregating mutation;

when the p-value is less than 0.05, calculating, for each potential carrier that has offspring with information about tumor multiplicity, a LOD score for presence of the segregating mutation, wherein the LOD score is $\log_{10}$ of a ratio of the probability of offspring phenotype data if the potential carrier mouse carries a multiplicity modifier to the probability of offspring phenotype data if the potential carrier mouse does not carry a multiplicity modifier, and wherein the denominator probabilities are calculated from an estimated background distribution and the numerator probabilities are calculated from a mixture of the estimated background distribution and an estimated modified distribution, where the estimated distributions are obtained by the method of maximum likelihood; and

mapping LOD scores of the potential carriers, whereby animals having the highest LOD scores are likely carriers of the segregating mutation.

28. A method as claimed in claim 26, further comprising the step of mapping the segregating mutation in the N2 backcross progeny using a mapping partner strain.

29. A method as claimed in Claim 28 wherein the mapping partner strain is produced by the steps of:

treating a C57BL/6 mouse with a mutagen to introduce random point mutations;

crossing the treated mouse to a C57BL/6 mouse to produce F1 progeny; and

sib-mating F1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.